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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUI, SAN MING R	
ART UNIT	PAPER NUMBER
1617	12

DATE MAILED: 04/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,994	MCKEARN ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *116-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *116-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The instant application claims the benefits of provisional US application Serial 60/113,786, filed December 23, 1998. The instant application is also a 371 of PCT/US99/30670.

Election/Restrictions

Applicant's election of the neoplastic agent as tamoxifen, the integrin antagonists as (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine, and the neoplasia as breast cancer in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's amendments filed March 25, 2003 have been entered. The cancellation of claims 1-115 in amendments filed March 25, 2003 is acknowledged. The addition of claims 116-118 in amendments filed March 25, 2003 is also acknowledged.

Claims 116-118 are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 116 and 117 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the instant case, the specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

The claims are very broad. In the instant specification, page 16, lines 3-11 discloses:

"The term "prevention" includes either preventing the onset of clinically evident neoplasia altogether or preventing the onset of a preclinically evident stage of neoplasia in individuals at risk. Also intended to be encompassed by this definition is the

prevention of initiation for malignant cells or to arrest or reverse the progression of premalignant cells to malignant cells." [emphasis added]

The instant claims are drawn to a method of preventing all preclinical stages of breast cancer, which include any undetectable stages of malignancy. The instant specification also fails to provide any guidance as to selecting the appropriate patient population. It is known in the art that various factors are involved in causing breast cancer in an individual. These factors include genetics, prolonged use of estrogen replacement, age, and environmental factors, such as diet (See Merck Manual, 16th ed., 1992, page 1815-1816). Without sufficient guidance, one of skilled in the art would be required to perform undue experimentation in order to practice the instant invention. Furthermore, the instant specification provides no working example of employing integrin antagonist to prevent the development of breast cancer. The nature of the invention is to prevent breast cancer by employing the herein claimed integrin antagonist and tamoxifen together or optionally, further combine with radiation therapy. However, radiation exposure would actually increase risk of developing breast cancer (See Merck Manual, page 1816, last paragraph). It is not clear how or why one of skilled in the art would use radiation therapy on individual who is only at risk for having breast cancer and is otherwise healthy. Moreover, the current known treatment of breast cancer is limited to hormonal, surgical, radiation, and chemotherapy (See Merck Manual, particularly, page 1818 to 1821). There is no preventive treatment so far. It is clear from the evidence of Merck Manual that the ability to prevent breast cancer is highly unpredictable and has met with very little success. Applicants have not provided

any convincing evidence that their claimed invention is indeed useful as preventive for breast cancer and have not provided sufficient guidance to allow one skilled in the art to practice the claimed invention without undue experimentation. In the absence of such guidance and evidence, the specification fails to provide an enabling disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 116 and 117 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "a mammal in need of such ... prevention" in claims 116 and 117 renders the claims indefinite because it is unclear who would be encompassed by the claims and be considered as "mammal in need of such prevention", and thus, the metes and bounds of the claims are not defined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 116 and 118 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rogers et al. (US Patent 6,013,651) in view of Brooks et al. (J. Clin. Invest., 1995, 96:1815-1822) and Goodman (Goodman & Gilman's the pharmacological Basis of Therapeutics, 9th ed., 1996, page 1275-1276, and 1424-1426), insofar as they relate to the treatment of breast cancer.

Rogers et al. teaches the elected compound, (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine, as a preferred integrin $\alpha_v\beta_3$ antagonist useful for treating tumor metastasis and solid tumor growth (See col. 7, compound (XXIX), also col. 8, line 4-15; claims 3, 6, 9, 12, and 15).

Rogers et al. does not expressly teach the employment of (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine in a method and combination to treat breast cancer. Rogers et al. does not expressly teach the incorporation of tamoxifen into the method and combination of treating breast cancer.

Brooks et al. teaches that $\alpha_v\beta_3$ plays a significant role in human breast cancer growth and the angiogenesis of human breast cancer cells (See the abstract). Brooks et al. teaches $\alpha_v\beta_3$ antagonist is useful in inhibit the human breast cancer growth (See the abstract). Brooks et al. further teaches that $\alpha_v\beta_3$ antagonist may provide an effective antiangiogenic approach for the treatment of human breast cancer (See the abstract; page 1820, col. 2, second paragraph-page 1821, first paragraph).

Goodman teaches that tamoxifen is useful as a systemic adjuvant therapy for breast cancer with surgery or chemotherapy (See page 1425, col. 2, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employment of (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine and tamoxifen in a method and combination to treat breast cancer.

One of ordinary skill in the art would have been motivated to employment of (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine and tamoxifen in a method and combination to treat breast cancer. Integrin $\alpha_v\beta_3$ antagonist is known to be useful in treating breast cancer. Therefore, employing any known $\alpha_v\beta_3$ antagonist, including (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine, in a method to treat breast cancer would be reasonably expected to be effective. Furthermore, tamoxifen is known to be useful as an adjuvant therapy for breast cancer with other chemotherapy. Therefore, incorporating tamoxifen with (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-

pyrimidinyl)amino]-benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine, which both are useful for treating breast cancer, in the method and combination for treating breast cancer would be reasonably expected to be effective (See MPEP 2144.06 and *In re Kerkhoven* 205 USPQ 1069) .

Claim 117 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rogers et al. in view of Brooks et al. and Goodman as applied to claims 116 and 118 above, and further in view of Merck Manual, 16th ed., 1992, page 1815-1821, insofar as they relate to the treatment of breast cancer.

Rogers et al., Brooks et al. and Goodman suggest the employment of (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine and tamoxifen in a method of treating breast cancer.

Rogers et al., Brooks et al. and Goodman do not suggest the incorporation of radiation therapy in the breast cancer treatment method.

Merck Manual teaches that radiation therapy as the primary treatment for breast cancer (See page 1818, fourth paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ radiotherapy with (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine and tamoxifen in a method of treating breast cancer.

One of ordinary skill in the art would have been motivated to employ radiotherapy with (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine and tamoxifen in a method of treating breast cancer because radiotherapy is known to be a primary treatment of breast cancer. Incorporating radiotherapy, (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine and tamoxifen, which are useful in treating breast cancer individually, together in a method of treating breast cancer would be reasonably expected to be effective (See MPEP 2144.06 and *In re Kerkhoven* 205 USPQ 1069).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
Patent Examiner
Art Unit 1617
April 16, 2003